Malignancy in coeliac disease – effect of a gluten free diet

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SUMMARY   Two hundred and ten patients with coeliac disease previously reported from this unit were reviewed at the end of 1985 after a further 11 years of follow up. The initial review at the end of 1974 could not demonstrate that a gluten free diet (GFD) prevented these complications, probably because the time on diet was relatively short. The same series has therefore been kept under surveillance with the particular aim of assessing the effects of diet on malignancy after a further prolonged follow up period. Twelve new cancers have occurred: of which one was a carcinoma of the oesophagus and two lymphomas. Thirty nine cancers developed in 38 patients and of 69 deaths, 33 were the result of malignancy. A two-fold relative risk (RR) of cancer was found and was because of an increased risk of cancer of the mouth and pharynx (RR=9·7, p<0·01, 95% confidence interval (CI)=2·0−28·3), oesophagus (RR=12·3, p<0·01, CI=2·5−36·5), and of non-Hodgkin's lymphoma (RR=42·7, p<0·001, CI=19·6−81·4). The results indicate that for coeliac patients who have taken a GFD for five years or more the risk of developing cancer over all sites is not increased when compared with the general population. The risk is increased, however, in those taking a reduced gluten, or a normal diet, with an excess of cancers of the mouth, pharynx and oesophagus (RR=22·7, p<0·001), and also of lymphoma (RR=77·8, p<0·001). A significant decreasing trend in the excess morbidity rate over increasing use of a GFD was found. The results are suggestive of a protective role for a GFD against malignancy in coeliac disease and give further support for advising all patients to adhere to a strict GFD for life.

There are several reports of an association between steatorrhoea and intestinal lymphoma which have been recently summarised.[1] The malabsorption was attributed in the early literature to lymphatic obstruction by enlarged mesenteric glands[2,3] but abnormalities in the small intestinal mucosa were also thought to play a part.[4] In reports up to 1961, the steatorrhoea in every case was considered to occur secondary to the lymphoma.

In 1962, Read and his colleagues from Bristol[5] suggested that lymphoma was a complication of coeliac disease in which the mucosal abnormality was a premalignant condition. They produced further

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evidence for this idea,[6] while in Birmingham the prevalence of lymphoma was shown to be statistically increased in coeliac diease and idiopathic steatorrhoea.[7] This report also drew attention to the increased risk of developing gastrointestinal carcinoma in general and oesophageal carcinoma in particular. Cancer of the small bowel is also a recognised association[8] and this observation was confirmed by the British collaborative study of coeliac disease and malignancy.[9]

At the end of 1974 a series of 210 patients with coeliac disease from the Gastroenterology Unit at the General Hospital, Birmingham, was analysed with regard to malignant complications and the effect on these of a gluten free diet (GFD).[10] A statistically significant increase in deaths from cancer occurred in the whole series and in men and women separately.

An increase was noted in deaths from lymphoma in men and women and in oesophageal and pharyngeal cancer in men. It could not be demonstrated that a GFD was effective in preventing malignant complications and only a longer follow up of patients on diet is likely to answer this vital question. The same series has, therefore, been kept under surveillance to document any further cancers and to further assess the effects of a GFD on the development of malignancy during this prolonged follow up period.

Methods

PATIENTS

The 210 patients with coeliac disease reviewed at the end of 1974 were re-evaluated at the end of 1985 with regard to age, sex, date of onset of symptoms, date first seen at the Gastroenterology Unit, and date of jejunal biopsy diagnosis. The strictness and duration of a GFD were recorded. The diagnosis of coeliac disease was based on the demonstration of a flat jejunal mucosa.[11] All malignancies occurring in the series were noted according to date of diagnosis, site, and histological diagnosis. This information was gathered directly from patients, from the case notes, the general practitioner and the Birmingham and West Midlands Cancer Registry. Where death had occurred, the date, autopsy result and death certificate were obtained. Patients who had defaulted from the clinic were traced from Family Practitioner Committee records and the National Health Service Central Register at Southport.

DIETARY GROUPS

Patients with coeliac disease vary greatly in their adherence to a GFD. If a GFD is capable of reducing the risk of developing malignant complications, it seems reasonable to assume that those patients who adhere to a strict GFD for a long period of time would be less at risk than those who have taken the diet for a short period or who have consumed some gluten or a normal diet.

The series was divided initially into three groups to reflect the degree of exposure to gluten. One group consisted of patients who had kept to a strict GFD for five or more consecutive years. The five year limit was an arbitrary decision before the analyses were carried out. This group included 108 patients satisfying the five year criterion. Eighty three patients (77%) had started GFD within five years of the date first seen in the clinic and 87% within 10 years. The remaining 14 patients started GFD at varying periods but once started tended to remain on the diet until death, only three patients exiting alive from the analysis with less than 10 years on GFD. This was the 'strict GFD group'. A group of 46 patients had no

record of a GFD and was designated the 'normal diet group'.

Among the remaining 56 patients, 15 had received a GFD for less than five years and an additional two patients were recorded as taking a GFD but the duration was unknown. For the remaining 39 patients the records showed only spasmodic use of the diet, duration of the GFD periods and the strictness of gluten exclusion being uncertain. It was therefore impossible to evaluate gluten free years. This group of 56 patients was designated the 'reduced gluten group'.

There was little difference between the groups in the mean interval from onset of symptoms to the date first seen in the clinic, the range being 12 years for the 'normal diet group' and 10 years for the 'strict GFD group'.

Analysis in terms of these three groups showed little difference, with respect to relative risks, between the 'normal diet group' and the 'reduced gluten group'. Because of the small numbers in these latter two groups they have been combined for most of the analyses and designated group 2 and have been compared with group 1, the strict GFD group, as defined above.

STATISTICAL METHODS

A cohort analysis was carried out to ascertain the risk of cancer morbidity in the series relative to that in the general population. The period at risk was measured from the date first seen at the Gastrointestinal Unit to the end of 1985. Patients dying before this date were withdrawn at the date of death. Those lost to follow up were included up to the date last known alive. To compute the numbers of cancers that might be expected to occur in the series, person-years at risk were multiplied by the appropriate sex, age and site specific incidence rates for cancer for two calendar periods standardised to the 8th Revision of the International Classification of Diseases (ICD 8), in the West Midlands Region. Expected numbers were obtained for all and individual sites of cancer using a modification of the MANYEARS program.[12] Assuming that the observed cancers follow a Poisson distribution, the significance of the differences between observed and expected numbers were calculated using the exact Poisson probabilities for a 1-tailed test. Excess morbidity rates (EMR) were also computed as 'observed – expected number/person-years at risk (PYR)' and the trend over diet group was tested.[13]

Results

INITIAL REVIEW (AT THE END OF 1974)

When the 210 patients were reviewed at the end of

1974, 13 had developed lymphoma all of whom were dead. Six patients with gastrointestinal cancer had also died as had two with other malignancies. These 21 deaths included eight in which the interval between the diagnosis of coeliac disease and malignancy was one year or less. In addition there were seven patients with malignancy who were still alive, and three diagnosed with a malignancy before first attendance at the clinic. When deaths from all malignancies were analysed, a statistically significant increase occurred in deaths from cancer both in the whole series and in men and women separately. An increase was found in deaths from lymphoma in men and women and in oesophageal and pharyngeal cancer in men. The deaths were also analysed in relation to dietary history but there was no evidence that a GFD (entered as a yes/no variable) was effective in preventing malignant complications. The full analysis of these patients has been reported previously.[10]

PRESENT REVIEW (AT THE END OF 1985)
This same series of patients was followed up and reviewed at the end of 1985. The three malignancies mentioned above which occurred before the diagnosis of coeliac disease were excluded from consideration. One other patient was originally thought to have carcinoma *in situ* in the skin and in a rectal polyp and was not included in the cancer group in the 1974 review. The panel of pathologists involved in the large collaborative study of coeliac disease and malignancy set up in 1978,[9] however, rechecked the histological slides and considered that the skin lesion was invasive. This patient, therefore, has now been added as a cancer case. For the whole group of 210 patients the male:female ratio was 1:1·2, the men contributing a mean of 17·4 person-years at risk and the women 19·4 years. The minimum possible follow up was 13 years (end of 1972 to end of 1985). One patient had emigrated and three could not be traced giving an overall follow up of 98%. Of the 69 deaths in the series, 33 were the result of cancer. A further five patients with malignancy were still alive. One patient had two tumours making 39 cancers in 38 patients. The analysis at the end of 1974 included the eight patients, all dead, in whom the interval between the diagnosis of coeliac disease and malignancy was one year or less. For the present review these have been excluded together with the expected numbers for the first year, from statistical consideration, leaving 31 tumours in 30 patients for the analysis.

A two-fold relative risk of cancer was found in the series as a whole, the difference between observed and expected numbers being highly significant (RR=2·0, p<0·001, 95% confidence interval (CI) of RR=1·4–2·8). The excess was because of increased

Table 1 *Cancer morbidity in 210 patients with coeliac disease at the end of 1985*

Site of cancer	ICD8	O	E	O/E	p
All sites	140–208	31	15·48	2·0	‡
Mouth and pharynx	141–147	3	0·31	9·7	†
Oesophagus	150	3	0·24	12·3	†
Non-Hodgkin's lymphoma	200, 202	9	0·21	42·7	‡
GI Tract	151–154	3	3·07	1·0	NS
Remainder		13	11·65	1·1	NS

O=observes numbers; E=expected numbers. †p<0·01; ‡p<0·001.

risk of cancers of the mouth, pharynx, oesophagus, and of non-Hodgkin's lymphoma. No other individual site showed an excess risk and the relative risks for the other gastrointestinal tract tumours and all other sites were close to 1·0 (Table 1). The relative risks for cancers of the mouth and pharynx and for the oesophagus were similar, being 9·7 (95% CI 2·0–28·3) and 12·3 (95% CI 2·5–36·5) respectively. Although the confidence intervals are wide, both sites showed a lower limit of around two-fold. The cancers in the mouth and pharynx were one tongue, one soft palate, and one pharynx. All three cancers of the oesophagus were squamous cell carcinomas. A highly significant excess of non-Hodgkin's lymphoma was evident (RR=42·7, p<0·001, CI 19·6–81·4). Again the confidence limits were wide but the lower estimate is still of the order of 20-fold.

CANCERS ARISING IN THE LAST 11 YEARS
The series has also been analysed to examine cancer incidence during the last 11 years from the end of 1974 to the end of 1985. Up to the last review 19 cancers were diagnosed (only those tumours diagnosed one year or more after the diagnosis of coeliac disease are considered). At the three sites of interest, 12 cancers were observed for an expected number of 0·37 (Table 2). Since 1974 a further 12 cancers occurred at all sites compared with 8·10 expected. Despite the lack of significance for the latter ratio of 1·5, it is not significantly different from the pre-1975 figures of 2·6 ($\chi^2_{(1)}$ corrected=1·78). Among the sites of interest two further lymphomas and one cancer of the oesophagus have occurred compared with 0·40 expected (RR=7·5, p<0·01). The relative risk is lower than that found for these sites pre-1975 (a 32-fold increase) and the difference in the ratios for the two periods is of borderline significance ($\chi^2_{(1)}$=4·73, p<0·05).

CANCER IN RELATION TO GLUTEN FREE DIET
When the diet groups were analysed separately (Table 3) the risk of cancer over all sites was not significantly increased for the 'strict GFD group'

Table 2   *Occurrence of malignancy from the end of 1974 to the end of 1985*

	-31/12/74				1/1/75 to 31/12/85			
Site of cancer	O	E	O/E	p	O	E	O/E	p
All sites	19	7·38	2·6	‡	12	8·10	1·5	–
Mouth and pharynx	3	0·16	19·4	‡	0	0·16	–	–
Oesophagus	2	0·11	18·7	†	1	0·13	7·5	–
Non-Hodgkin's lymphoma	7	0·10	67·3	‡	2	0·11	18·9	†
Remainder	7	7·01	1·0	–	9	7·66	1·2	–

†p<0·01; ‡p<0·001.

Table 3   *Cancer morbidity by diet group*

Site of cancer	Diet group	N	O	E	O/E	p
All sites	1	108	14	9·06	1·5	–
	2	102	17	6·42	2·6	‡
Mouth, pharynx oesophagus	1	108	1	0·33	3·0	–
	2	102	5	0·22	22·7	‡
Non-Hodgkin's lymphoma	1	108	2	0·12	16·7	†
	2	102	7	0·09	77·8	‡
Remainder	1	108	11	8·61	1·3	–
	2	102	5	6·11	0·8	–

†p<0·01; ‡p<0·001.

(group 1). The risk was significantly increased in those taking a normal diet or a reduced gluten diet (group 2). The small excess in group 1 was accounted for mainly by the occurrence of two non-Hodgkin's lymphomas (RR=16·7, p<0·01). The patients receiving a normal diet or a reduced gluten diet (group 2), showed an excess of cancers of the mouth, pharynx, and oesophagus (RR=22·7, p<0·001), and also of lymphoma (RR=77·8, p<0·001). Although no difference between the groups could be detected for individual sites, on combining them (mouth, pharynx, oesophagus, and lymphoma), the difference between the relative risks – 6·7 for group 1 and 38·7 for group 2 – was statistically significant ($\chi^2_{(1)}$= 4·53, p<0·05). When the results were distributed into the original three diet groups (Table 4), a significant decreasing trend in EMR over increasing use of GFD was found. The numbers are relatively small and a linear scale for GFD was used.

Patients in group 1 had remained on a GFD for a mean of 16·7 years (range five to 34 years, median 16 years). The two lymphomas arising in the group occurred at a time when the average duration on a GFD was seven years. Among patients surviving 10 or more years the mean duration on a GFD was 17·3 years. No lymphoma was observed during this period (Table 5). In those patients who did not adhere to a strict GFD (group 2), however, the risk of lymphoma was highly significantly increased before and after the 10 year point of follow up. The numbers of patient-years at risk in each group during the 10+ years of

Table 4   *Cancer morbidity by three diet groups in mouth, pharynx, oesophagus, and lymphoma*

Diet group	N	O	E	O/E	EMR[+]/10⁵ PYR
Normal diet	46	7	0·19	36·8‡	10·7
Reduced gluten diet	56	5	0·12	41·7‡	5·0
Strict GFD	108	3	0·46	6·5*	1·2

Trend for EMR over diet group: χ^2_1=9·9, p<0·01.
*p<0·05; ‡p<0·001.
[+]EMR=excess morbidity rate (O–E/PYR×10⁵).

Table 5   *Incidence of lymphoma by diet group and follow up years*

	Years of follow up								
	1–9					10+			
Diet group	N	O	E	O/E	p	N	O	E	O/E	p
1	108	2	0·04	44·4	‡	100	0	0·08	–	–
2	102	3	0·03	100·0	‡	74	4	0·05	80·0	‡

‡p<0·001.

follow up were comparable – group 1 = 1098·9, group 2 = 900·3.

Discussion

There is no doubt that patients with coeliac disease are at increased risk of developing malignancy, particularly lymphoma.[5-7 9 14-16] When the present series was reviewed at the end of 1974, 21 deaths had occurred from cancer when only five were expected.[10] Of these deaths 13 were the result of lymphoma with an expected incidence of 0·1. Significant increases in death from oesophageal and pharyngeal carcinoma were also found.

This same series was kept under review and at the end of 1985 of the 69 deaths which had occurred, 33 were caused by malignancy. Overall there were 39 cancers in 38 patients. The eight patients in whom the interval between the diagnosis of coeliac disease and malignancy was one year or less were not included in the statistical analysis because the development of malignancy was the event which may have led to the diagnosis of coeliac disease and could be a potential source of bias in the analysis. Nevertheless, these patients are of interest and fall into two groups. Six had histories of coeliac disease from six to 36 years (mean 21 years) although it was malignant complications which brought them to diagnosis. Of the remaining two patients one did not complain of any symptoms until nine months before death when they were attributed to malignancy, while the other had a two year history initially considered to be the result of coeliac disease but almost certainly induced by the

underlying cancer. Many observations which have been summarised recently all strengthen the concept that these patients presenting with malignancy and findings compatible with coeliac disease should be regarded as having coeliac disease complicated by malignancy.[17]

The increased risk of developing non-Hodgkin's lymphoma, cancer of the mouth, pharynx, and oesophagus was confirmed and overall there was a two-fold relative risk of cancer arising. The risk of coeliac patients in general, however, may well be lower as patients without symptoms or only mild ill-health may never present and so are excluded from calculations of prevalence. On the other hand there are patients with lymphoma who also have coeliac disease which may never be diagnosed.[18] No case of carcinoma of the upper jejunum was encountered in the series although one of us has encountered such patients elsewhere.[8] A British collaborative study found this to be the commonest malignancy of the gastrointestinal tract after non-Hodgkin's lymphoma which illustrates the value of pooling information from many centres.[9]

From the end of 1974 to the end of 1985 a further 12 cancers had occurred of which one was an oesophageal carcinoma and two were lymphomas. The analysis showed a small difference in the cancer risk for the two follow up periods, which might be attributable to a decreased risk in those patients adhering to a GFD (group 1). The diagnosis of lymphoma complicating coeliac disease is difficult and may be delayed because the presenting features are often non-specific and indistinguishable from uncomplicated coeliac disease in relapse. In the great majority of patients the tumour is widely disseminated at diagnosis and hence the prognosis is very poor. In a third of cases in one series the diagnois was only made at autopsy.[14] Unexplained deterioration in a coeliac patient previously well controlled on a GFD should alert the clinician and the development of weight loss, muscle weakness, pyrexia and lymphadenopathy should always raise the suspicion of lymphoma. The newly diagnosed adult coeliac patient requires careful observation for among one reported group one in 20 had developed lymphoma within four years of the diagnosis of coeliac disease. Over the age of 50 years the risk was one in 10.[19]

While patients with lymphoma often have abnormal haematological and biochemical indices there is no pattern of abnormality which enables lymphoma to be diagnosed early. Quantitative changes in the inflammatory cell infiltrate of the small intestinal mucosa have been described in those patients who eventually develop malignancy which differ from those who do not.[20 21] A prospective study has never been mounted, however, and these obser-vations, even if true, are unlikely to be helpful in the individual case.

As the diagnosis of lymphoma in coeliac disease still poses formidable difficulties which are unlikely to be surmounted in the near future, the question arises, can this complication be prevented by strict adherence to a GFD? Our earlier study using a simple yes/no variable failed to show whether or not a GFD was protective in preventing malignant complications. This was not surprising if protection is dependent on duration and strictness of the diet as the average time spent on diet was only 7·5 years. The same series of patient was, therefore, kept under review so that a longer follow up might help to answer this important question. The results from the present study suggest that a GFD may influence the subsequent development of malignancy. In patients who have taken a strict GFD for more than five years (group 1), the overall cancer risk is not significantly increased while there is a significantly increased risk among patients on a normal or reduced gluten diet (group 2). Two lymphomas occurred in the strict GFD group which may indicate that in such cases the relatively short time on diet is insufficient to reverse the effects of exposure to an oncogenic stimulus, which has operated for many years, probably from infancy. Alternatively factors other than gluten may influence the development of malignancy in some cases. When the two diet groups were compared with regard to mouth, pharynx, oesophagus, and lymphoma combined, a significant difference emerged and the excess risk is associated with the amount of gluten ingested.

These results would appear to support a protective role for a GFD with regard to malignancy complicating coeliac disease and is a further reason for advising all patients to adhere to a strict diet for life.

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